

Consensus Guidelines

Consensus for Radiotherapy in Hepatocellular Carcinoma from The 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014): Current Practice and Future Clinical Trials

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Key Words

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Abstract

A consensus meeting to develop practice guidelines and to recommend future clinical trials for radiation therapy (RT), including external beam RT (EBRT), and selective internal RT (SIRT) in hepatocellular carcinoma (HCC) was held at the 5th annual meeting of the Asia-Pacific Primary Liver Cancer Expert consortium. Although there is no randomized phase III trial evidence, the efficacy and safety of RT in HCC has been shown by prospective and retrospective studies using modern RT techniques. Based on these results, the committee came to a consensus on the utility and efficacy of RT in the management of HCC according to each disease stage as follows: in early and intermediate stage HCC, if standard treatment is not compatible, RT, including EBRT and SIRT can be considered. In locally advanced stage HCC, combined EBRT with transarterial chemoembolization or hepatic arterial infusion chemotherapy, and SIRT can be considered. In terminal stage HCC, EBRT can be considered for palliation of symptoms and reduction of morbidity caused by the primary tumor or its metastases. Despite the currently reported benefits of RT in HCC, the committee agreed that there is a compelling need for large prospective studies, including randomized phase III trial evidence evaluating the role of RT. Specifically studies evaluating the efficacy and safety of sequential combination of EBRT and SIRT are strongly recommended.

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Introduction

Hepatocellular carcinoma (HCC) presents one of the most important therapeutic challenges in oncology and it is the second leading cause of cancer-related death world-wide [1]. At the time of diagnosis, more than two-thirds of patients with HCC are not eligible for curative treatments. In the Barcelona Clinic Liver Cancer (BCLC) staging system, which is widely used to recommend treatment modalities for the different stages of HCC, trans-arterial chemoembolization (TACE) is recommended for intermediate stage disease (BCLC B, which includes patients with large multinodular, Child-Pugh A-B, and performance status 1-2), this being the most common stage of the disease at the time of diagnosis. This recommendation for TACE is based on clinical experience and positive results from meta-analyses [2–4], but there remain controversies about the optimal indications for TACE and the timing of conversion to other alternative treatments [5–7]. Sorafenib is the only other recommended treatment recommended by BCLC based on the reported survival advantage from randomized trials against placebo [8, 9]. The modest overall survival benefits of sorafenib (approximately 2.5 months) and minimal response rates raises questions about whether its use as monotherapy is appropriate when the cancer is not metastatic.

Radiation therapy (RT) is one of the main treatment modalities for cancer. Historically, RT was regarded as ineffective in HCC because of the limitation of RT dose that could be delivered and this in turn was related to the radiation sensitivity of surrounding non-malignant liver parenchyma and previously limited RT techniques [10].

With recent advances in external beam RT (EBRT) technique, including 3-dimensional conformal RT (3D-CRT), intensity modulated RT (IMRT), stereotactic ablative body RT (SABR), and/or image-guided RT, the delivery of higher RT doses to achieve acceptable local

control has become possible [11, 12]. Additionally, accounting for and managing respiratory motion by several methods including compression, gating, or tracking, reduces the possibility of mistargeting as well as unnecessary additional RT exposure to surrounding normal organs and tissues.

Recent research on the radiation biology of HCC, normal liver, and adjacent normal organs also allows greater leeway for RT to be used safely in HCC [13–15]. Recently, multiple prospective as well as retrospective studies have reported positive outcomes of RT with 40 to 70% response rates, and favorable overall survival as well as good local control rates [16–19].

Similarly selective internal RT (SIRT) uses radioisotopes to deliver high dose but short range radiation (less than 1 cm) by transarterial radioembolization (TARE). SIRT is another form of RT that can obtain higher local control with minimal concerns for toxicity to the surrounding liver and promising results have also been reported [20–23].

The fifth annual meeting of Asia-Pacific Primary Liver Cancer Expert, a consortium of liver cancer specialists from the Asia-Pacific, which included hepatologists, surgeons, radiologists, radiation oncologists, medical oncologists, and pathologists was held from July 11 to 13, 2014 in Taipei, Taiwan [24]. A committee of 13 experts and key opinion leaders from the Asia-Pacific region met to develop consensus practice guidelines pertaining to the use of RT, (both EBRT and SIRT) in unresectable HCC.

Eight radiation oncologists, two interventional radiologists, one hepatologist, and two surgeons participated in the deliberations on RT in HCC. Five experts presented the outcomes of clinical studies and their expert opinions on the first day (11 July); these extensive materials were then summarized by two representatives and shared with the other experts. After active discussions, consensus was reached on recommendations for RT in HCC on the second day (12 July). The complete consensus practice guidelines were finalized after further discussions and were shared with all members of the committee on the third day (13 July).

In this report, we present the consensus practice guidelines and recommendations on pivotal future clinical trials of RT in HCC arrived at by clinical experts and key opinion leaders in the Asia-Pacific region.

Grading System for the Consensus

In this consensus development, levels of evidence were stratified by the modified Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system [25, 26]. The outline of the GRADE system is shown in table 1. Briefly the quality of evidence is classified as high (A), moderate (B), and low (C) according to the possibility of changes in the estimate of the clinical effects by further research. The strength of recommendation is divided as strong (1) and weak (2) according to factors including the quality of the evidence, presumed patient-important outcomes, social resources, and cost.

EBRT in HCC

Historical Avoidance of RT in HCC Management

As described above, RT had historically a minimal role in the management of HCC and was limited to the palliative treatment of extra-hepatic metastatic lesions. The most crucial hurdle to RT application in HCC was the relatively poor radiation tolerance of surrounding regions of the liver [27]. Radiation induced liver disease (RILD), a dreadful complication associated with increased risk of death, has been reported even after very limited radiation doses with

Table 1. GRADE

Quality of evidence	Criteria
High (A)	Further research is unlikely to change confidence in the estimate of the clinical effect
Moderate (B)	Further research may change confidence in the estimate of the clinical effect
Low (C)	Further research is very likely to impact confidence on the estimate of the clinical effect
Strength of recommendation	Criteria
Strong (1)	Factors influencing the strength of the recommendation including the quality of the evidence, presumed patient-important outcomes, and cost
Weak (2)	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption

Of the quality levels of evidence, we excluded "very low quality (D)" in our guideline for convenience, which was originally included in the GRADE system and indicates that any estimate of effect being very uncertain.

2-dimensional RT technique [28]. Liver cirrhosis which is usually related to the development of HCC is a likely reason that the liver is more fragile to RT [29]. Due to the importance of maintaining good liver function in the management of HCC, until recently, RT could not be justified against this background. Concerns regarding radiation-induced bowel toxicity were also an important obstacle to delivering sufficient RT dose [30–32].

Techniques of EBRT

With the application of computed tomography (CT) simulation in RT, more precise and accurate dose delivery has become possible. More comprehensive research on RILD after RT also became possible with dose-volume histogram analysis from 3D-CRT planning [13–15, 29]. With a deeper understanding of the occurrence RILD and more conformal delivery of RT, RILD has become rarely reported in the recent liver-centric RT literature.

While maintaining an acceptable risk of RILD, about 40 to 60% response rates have been achieved with irradiation dose escalation [16, 18, 33]. This RT dose-response relationship has been repeatedly recognized in several studies [17, 34, 35]. Additionally, the overall survival advantage of RT over best supportive care or other modalities in advanced HCC has been reported by meta-analyses as well as several retrospective comparison studies [36–38].

IMRT which is an even more conformal delivery method of RT is increasingly used in solid tumors of nearly all sites of the body [39]. Through strict dose constraints according to the method of inverse planning, IMRT permits more conformal and higher dose delivery in HCC [40, 41]. Dose escalation of RT with IMRT has been achieved without significant incremental toxicity and has delivered better survival compared with 3D-CRT, which have been verified in several studies [42, 43]. IMRT can also be effectively used to escalate the RT dose in the tumor in proximity to small and/or large bowel, which acts as a dose limiting organ on occasion [42].

Although several guidelines or consensus surveys of SABR have been reported [44–47], there has been no clear and precise definition of SABR. The precise and accurate ablative radiation dose delivery of a relatively large single dose with less than five fractions is generally accepted as SABR [39]. Because of the excellent local control possible with this technique in HCC [48–50], this is currently under active investigation and there has been a dramatic increase in the number of registered prospective SABR protocols on the clinicaltrials.gov

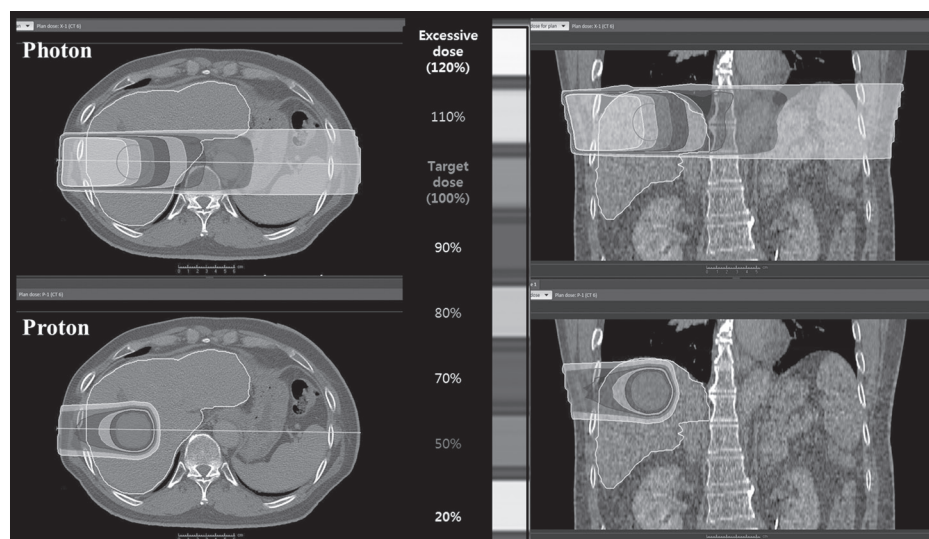


Fig. 1. Schematic isodose curves of single beam proton and photon beam RT planning. Unnecessary dosing is largely exposed in photon beam than proton beam in this planning, though multiple conformal beam arrangement is routine with three-dimensional or intensity modulated technique in real practice of HCC treatment.

[51]. A survey of the rapid adoption of SABR for HCC in Korea revealed SABR usage just in four institutions in 2007 and but as many as 31 institutions by 2013 [45].

A large, prospective phase I/II trial evaluating the efficacy and safety of SABR in 102 patients with locally advanced HCC reported that they demonstrated a favorable local control rate of 87% at one year with a median overall survival of 17.0 months [52]. Grade III or higher toxicities have been seen in 30% of patients and have been comparable with other modalities of delivery.

Particle beams, including proton, and carbon are a totally different field of EBRT from conventional photon beams [39, 53]. Proton and carbon ions have a common superior characteristic over photons. They represent an outstanding dose distribution profile originating from their specific characteristics of Bragg peak [54]. The schematic explanation of Bragg peak of proton and usual photon beams in HCC is shown in fig. 1. So far, there has been no randomized trial confirming the superiority of these particles over photons. However, overwhelming theoretical and experimental advantages including a relative insensitivity to hypoxia and enhanced biological effects support the wide usage of protons and carbon ions in solid tumors of most parts of the body. Specifically in HCC, protons have been reported to show excellent local control and survival [55–57]. In fact, HCC is one of the cancers expected to receive the greatest benefit from the particle beam therapy. In addition, particle beam RT could be used even in HCC patients where photon beam RT and even SABR is contraindicated [58]. In Japan, 19 patients with HCC and Child-Pugh class C liver status who would otherwise have received only supportive care according to the BCLC staging system, because the lack of the liver donations precluded transplantation, were treated using proton beam therapy. After applying relatively high biologically equivalent doses of ≥ 75 gray (Gy) to these patients, favorable outcomes of 47% one-year progression free survival, and 53% one-year overall survival were reported without significant deterioration of liver function. However, although the number of facilities practicing particle beam therapy are increasing, resources and evidence of particle treatment in HCC are currently still limited. Therefore, the cost-benefit of particle beam RT in HCC should be studied in the near future.

Combined Treatment of RT in HCC Management

Combination treatment with RT is an area of active study in HCC. TACE and hepatic arterial infusion chemotherapy (HAIC) are the main combination agents to enhance RT and improve clinical outcomes, especially in locally advanced HCC with or without portal vein tumor thrombosis (PVT). In several prospective and retrospective studies, the role of selective radiation sensitizers of HCC have been demonstrated [18, 19, 59]. They have helped to reduce the total RT dose, thus reducing the possibility of complications without compromising local control and survival outcomes. RT also could potentially be utilized with systemic therapeutic agents. The combination of a targeted agent like sorafenib concurrently and/or sequentially with RT might obtain synergistic effect, potentially decreasing intrahepatic progression, which is the most important failure pattern of successful local RT [60]. Targeted therapeutics could ameliorate the effects of vascular endothelial growth factor, which is confirmed to increase after local RT [61].

RT Related Adverse Effects in HCC Management

RILD and gastroduodenal toxicities are important and worrisome RT related adverse events in patients with HCC [27, 30]. The exact threshold dose of RILD remains unclear. Based on recently reported studies however, RILD has rarely developed if RT exposure does not exceed 30 Gy to more than 60% of the total liver volume or 50% of the non-cancerous liver volume (total liver volume minus gross tumor volume), even in patient with liver cirrhosis [15, 16, 19].

Gastroduodenal toxicities are not uncommon in patients with HCC who are receiving RT. Symptomatic grade III toxicities are acceptable, which is found in less than 5% of treated patients if the exposed RT dose does not exceed 35 Gy to less than 5% of gastroduodenal volume [16, 31, 32].

Randomized Evidence of RT in HCC Management

Although there has been a significant number of prospective as well as retrospective studies on the clinical efficacy and safety of RT in the management of HCC, no phase III randomized trial has been reported so far. The Radiation Therapy Oncology Group 1112 trial, a well-designed multinational, randomized phase III trial, comparing sorafenib versus SABR followed by sorafenib, which is evaluating the role of RT in unresectable HCC, is ongoing. It will hopefully provide valuable information on this topic.

Consensus Guidelines of EBRT in HCC

In a multidisciplinary management setting, RT may be an effective treatment option for each stage of HCC (fig 2). Specific recommendations of RT according to the stage are as follows:

1. In early stage HCC, if resection, transplantation and radiofrequency ablation (RFA) are not accessible or feasible, SABR or hypo-fractionated 3D-CRT/IMRT can be considered (evidence level C1).
2. In intermediate stage HCC, if angiography is not practical, salvage RT can be considered instead. Consolidated RT can be considered in patients who are showing incomplete response to TACE (evidence level C1).
3. In locally advanced stage HCC, combined RT with TACE or HAIC can be considered (evidence level C1).
4. In HCC with oligo-metastases, high dose RT with potential curative intent can be considered (evidence level C1).
5. In terminal stage HCC, RT can be considered for palliation of symptoms and reduction of morbidity caused by primary HCC or its metastases (evidence level B2).

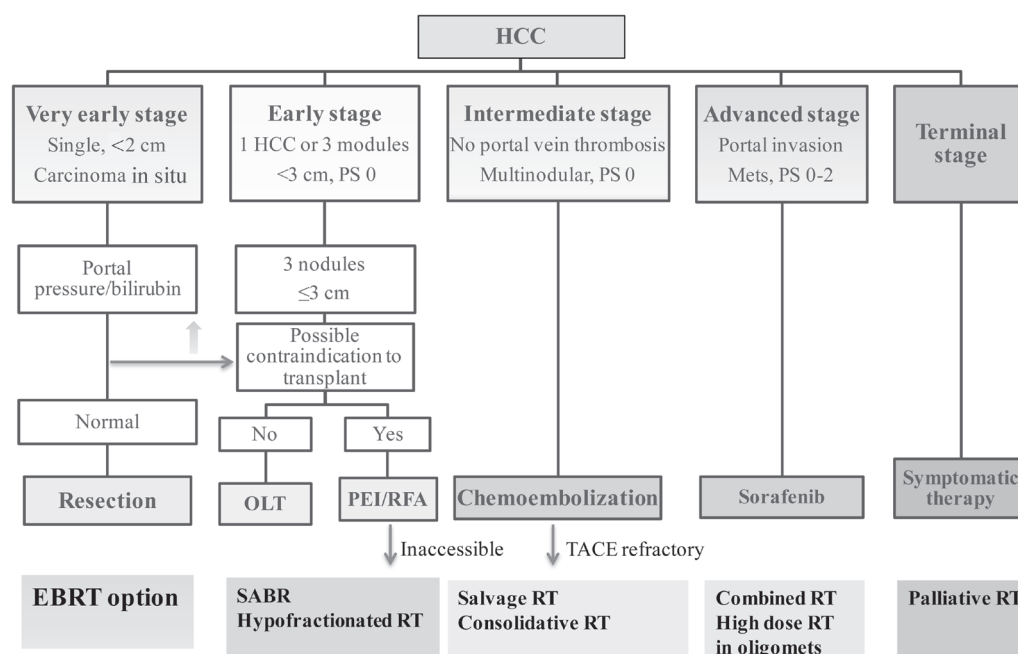


Fig. 2. Consensus practice guidelines for (EBRT) stratified by stage of cancer. OLT=orthotopic liver transplant; PEI=percutaneous ethanol injection; PS=performance status.

All members of the committee agreed that there is still insufficient high quality scientific evidence for EBRT in the treatment of HCC, and prospective studies evaluating the real effect of EBRT in each of the stages are warranted.

SIRT

SIRT, also known as TARE, or simply as radioembolization, is a form of RT delivery that utilizes selective transarterial administration of microspheres loaded with radioisotopes, like yttrium 90, iodine 121, or rhenium [62]. The short tissue penetration distance (average 2.5 mm, maximal 11 mm in Yttrium 90) which is mainly used in SIRT is ideal for brachytherapy and it avoids concomitant radiation damage to surrounding liver parenchyma. In SIRT, radiation is the main therapeutic mechanism rather than embolization in causing tumor cell death [62]. Members of the committee agreed that the term SIRT rather than TARE would be a more appropriate term describing its characteristics and identity.

As there has been no previously completed randomized phase III trial comparing SIRT against standard management, SIRT is not currently recommended in the BCLC guidelines [63]. However, potential advantages, like selective delivery of radiation, the high responsiveness of HCC to RT, and the probable superiority over standard treatment, like sorafenib, have been reported by several prospective as well as retrospective studies [20–23].

Patients with early stage HCC (BCLC A, which includes patients with single or less than 3 cm of 3 nodules, Child-Pugh A-B, and performance status 0) are candidates for potentially curative treatments such as resection, RFA and transplantation. Specifically, patients with HCCs with low tumor burden (within Milan Criteria) but with poor existing liver function which precludes resection, are ideal candidates for liver transplantation [63]. Although liver transplantation shows the most favorable outcome in such cases, the risk of disease progression

during the long wait for cadaveric transplantation consequent to a low number of donors, poses an important limitation in this strategy. Locoregional modalities that limits local progression in HCC are currently used as bridging therapy for such candidates on the transplant waiting list, and SIRT is proposed as one such valuable therapeutic option together with RFA, TACE, and SABR [64].

In intermediate stage HCC (BCLC B), TACE is the only validated and recommended treatment in the BCLC guidelines. In cases contraindicated for TACE or where TACE has poor efficacy, like in high tumor volume (multifocal and/or bilobar) HCC, or where HCC is refractory to TACE or who have progressed on TACE, SIRT has shown favorable survival outcomes with less incidence of adverse events compared to conventional TACE [22, 65]. In some patients with intermediate stage HCC, potentially curative treatments including hemihepatectomy can be considered. In that respect, RFA has been possible after down-staging of tumor with locoregional treatment. SIRT has shown more favorable results in terms of down-sizing and objective response compared to conventional TACE in several studies [66, 67].

In advanced stage HCC (BCLC C, which includes patients with portal vein invasion, or extrahepatic spread, Child-Pugh A-B, and performance status 1-2), sorafenib is the only recommended therapy in the BCLC guidelines based on the results of two phase III randomized trials [63]. Advanced stage HCC is a heterogeneous group and it includes patients with vascular invasion, distant metastases or both. While conventional TACE is considered a contraindication in HCC with tumor thrombosis of major portal veins, SIRT is not associated with a strong embolic effect and is not contraindicated [62]. Compared with the reported poor overall survival of 4.1 months for patients receiving sorafenib in HCC with PVTT, the median overall survival of SIRT is promising at 7.3 to 11.8 months in patients had Child-Pugh class B or A [21, 68–70].

While adverse events associated with SIRT are reportedly fewer and milder than TACE, there are other major complications specific to SIRT related to delivering a toxic RT dose to neighboring tissues, like RILD, gastrointestinal ulcers, pneumonitis, and biliary complications [71–74]. The risk of RILD or liver failure, may be increased in patients who have low tumor/normal liver ratio following radiation delivery [75]. Radiation-induced lung injury has been shown to develop in more than 50% of cases with significant hepatopulmonary shunts [72]. Therefore, low tumor/normal liver ratios and high hepatopulmonary shunts are contraindications to SIRT.

Consensus Guidelines of SIRT in HCC

In a multidisciplinary management setting, SIRT can be an effective treatment option for early to advanced stages of HCC (fig 3). Specific recommendations of SIRT according to the stage are as follows:

1. In early stage HCC, SIRT can be considered for bridging treatment for cadaveric liver transplantation (evidence level C1).
2. In intermediate stage HCC, SIRT can be considered for bilobar, multinodular or large tumour burden HCC, and also for HCC after conventional TACE has failed. There is limited data that SIRT may be used as neoadjuvant treatment (evidence level C1).
3. In advanced stage, SIRT can be used for patients with vascular invasion and liver-dominant metastatic HCC (evidence level C1).

All participants of the committee agreed that there is still a paucity of high level or phase III data for SIRT in HCC, and prospective studies evaluating the real effect of SIRT stratified by the stages of HCC should be carried out.

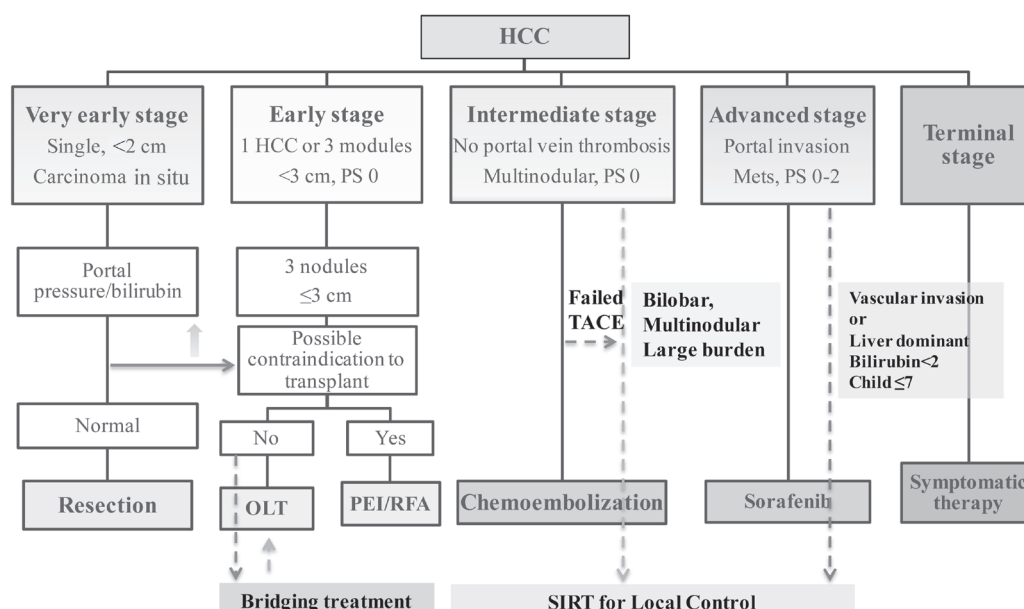


Fig. 3. Consensus practice guidelines for SIRT stratified by stage of cancer.

Conclusion and Recommendations for Future Trials

All members of the committee agreed there is currently an absence of completed randomized phase III trials comparing RT to standard treatment but noted that there are trials ongoing. They agreed that to evaluate the real role of RT, (EBRT and SIRT) in HCC, additional large prospective studies should be initiated.

Additionally, the results of EBRT including SABR, particle beam, and SIRT might be similar in terms of survival as well as response rate and local control, though SIRT is used in limited institutions with limited publications compared with EBRT [50, 76, 77]. Larger prospective and/or retrospective comparison studies comparing these two modalities stratified by stage are also needed to manage unresectable HCC more optimally.

The committee suggests that prospective trials evaluating the efficacy and safety of sequential combination of EBRT and SIRT are valid in advanced stage HCC with PVTT. It may be able to overcome the limitations of local control using EBRT or SIRT alone. However, a pilot study evaluating the safety of combined treatments should be conducted before a randomized study. The sequence and optimal interval of EBRT and SIRT should be also evaluated.

Disclosure Statement

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